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## Mixed $\kappa$ Agonists and $\mu$ Agonists/Antagonists as Potential Pharmacotherapeutics for Cocaine Abuse: Synthesis and Opioid Receptor Binding Affinity of *N*-Substituted Derivatives of Morphinan

John L. Neumeyer,<sup>a,\*</sup> Xiao-Hui Gu,<sup>a</sup> L. Alexander van Vliet,<sup>a</sup> Nicholas J. DeNunzio,<sup>b</sup>  
Daniela E. Rusovici,<sup>b</sup> Dana J. Cohen,<sup>b</sup> S. Stevens Negus,<sup>a</sup> Nancy K. Mello<sup>a</sup>  
and Jean M. Bidlack<sup>b</sup>

<sup>a</sup>Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA

<sup>b</sup>Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, NY 14642, USA

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**Abstract**—A series of new *N*-substituted derivatives of morphinan was synthesized and their binding affinity for the three opioid receptors ( $\mu$ ,  $\delta$ , and  $\kappa$ ) was determined. A paradoxical effect of *N*-propargyl (MCL-117) and *N*-(3-iodoprop-(2*E*)-enyl) (MCL-118) substituents on the binding affinities for the  $\mu$  and  $\kappa$  opioid receptors was observed. All of these novel derivatives showed a preference for the  $\mu$  and  $\kappa$  versus  $\delta$  binding. © 2001 Elsevier Science Ltd. All rights reserved.

The abuse of cocaine and other stimulant drugs is becoming a significant social and public health concern in the world.<sup>1</sup> Drug abuse has contributed greatly to the increasing spread of HIV and HBV.<sup>2</sup> Currently there are no efficacious medications for the treatment of cocaine abuse.<sup>3,4</sup> Although the mesolimbic dopamine pathway is believed to play a primary role in mediating the locomotor, discriminative stimulus and reinforcing effects of cocaine,<sup>5–8</sup> other neurotransmitter systems have also been implicated in the reinforcing effect of cocaine.<sup>9–15</sup>

There is increasing evidence that opioid receptor agonists are able to modulate the neurochemical and behavioral effects of cocaine. For example, kappa ( $\kappa$ ) receptor agonists attenuated cocaine-induced increases in dopamine levels in the nucleus accumbens.<sup>16,17</sup> Administration of  $\kappa$  opioid receptor agonists has also been reported to attenuate the discriminative stimulus properties,<sup>18–20</sup> conditioned reinforcing effects,<sup>21–23</sup> and self-administration of cocaine.<sup>24–28</sup> Further,  $\kappa$  opioid agonists attenuated the reinstatement of extinguished

drug-taking behavior in an animal model of relapse.<sup>26,29</sup> Taken together, these findings suggest that activation of  $\kappa$  opioid receptors may functionally antagonize some abuse-related effects of cocaine, possibly by inhibiting the release of dopamine from dopaminergic neurons, and thus offers a novel and effective pharmacological approach to treat cocaine abuse.

In recent studies, we found that the nonselective  $\kappa$  agonist ethylketocyclazocine (EKC), which possesses  $\mu$  receptor-mediated effects in addition to its  $\kappa$  agonist effects, decreased cocaine self-administration more effectively and with fewer undesirable side effects than highly selective  $\kappa$  agonists.<sup>27</sup> This suggested that non-selective  $\kappa$  opioid receptor agonists with additional activity at  $\mu$  opioid receptors may be especially useful for the treatment of cocaine abuse.

Our initial efforts to develop mixed  $\kappa$  agonists and  $\mu$  agonists/antagonists focused on the morphinan and benzomorphan nucleus, because derivatives of morphinan and benzomorphan such as cyclorphan and cyclazocine are known to have potent mixed activity at  $\mu$  and  $\kappa$  opioid receptors. As part of these efforts, we synthesized and pharmacologically evaluated some analogues of cyclorphan and cyclazocine.<sup>30,31</sup> From that study, we

\*Corresponding author. Tel.: +1-617-855-3388; fax: +1-617-855-2519; e-mail: neumeyer@mclean.harvard.edu

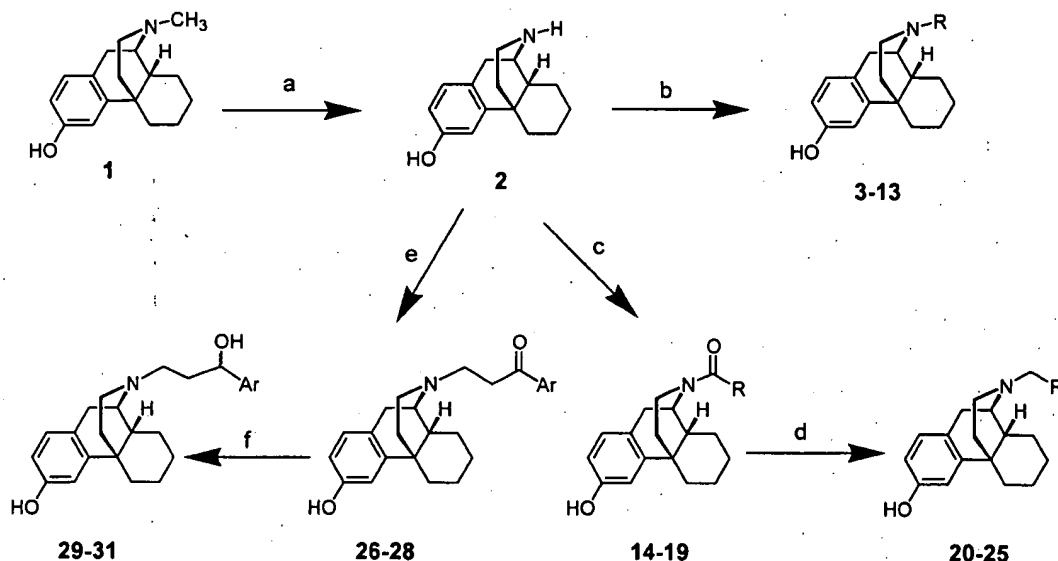
observed that morphinans with a cyclobutylmethyl or (*S*)-tetrahydrofurfuryl group on the nitrogen atom had  $\kappa$  agonist activity. In order to systematically study the effects of *N*-substituents in the morphinan nucleus on binding affinity, selectivity, and efficacy at  $\mu$  and  $\kappa$  opioid receptors, we introduced a variety of substituents on the nitrogen atom in morphinan. Herein, we report on the synthesis and preliminary biological evaluation of a series of *N*-substituted derivatives of morphinan.

The target derivatives 3–13 and 20–31 were synthesized from norlevorphanol 2 by one of the three methods as depicted in Scheme 1. Demethylation of levorphanol 1 was accomplished according to the procedure reported by DeGraw and Engstrom.<sup>32</sup> Thus, levorphanol was treated with ethyl chloroformate in refluxing chloroform in the presence of  $K_2CO_3$  followed by partial hydrolysis of the product with 10% NaOH in methanol. Norlevorphanol 2 was obtained in good yield after hydrolysis of the resulting carbamate (structure not shown) intermediate in a mixture of hydrochloric acid and glacial acetic acid. Direct alkylation of norlevorphanol with various alkyl halides in DMF using  $K_2CO_3$  or  $NaHCO_3$  as base provided *N*-substituted derivatives 3–13<sup>33</sup> in good to excellent yields. Alternatively, acylation of norlevorphanol with acid chlorides followed by reduction of the intermediate amides, 14–19 with  $LiAlH_4$  in THF afforded the tertiary amines 20–25. Alkylation of norlevorphanol with 1-aryl-3-(dimethylamino)-1-propanone methiodide in DMF in the presence of  $Na_2CO_3$  yielded ketones 26–28, which were then reduced with  $NaBH_4$  to afford the alcohols 29–31 as a mixture of hydroxy diastereomers. The *N*-(3-iodoprop-(2*E*)-enyl) and *N*-(3-iodoprop-(2*Z*)-enyl) derivatives 34 and 35 were obtained by iododestannylation of compounds 32 and 33 by treatment with iodine in chloroform (Scheme 2). The tributyltin precursors 32 and 33 were prepared by hydrostannylation of the *N*-propargyl derivative 9 with  $HSnBu_3$  in the presence of  $Et_3B$  as

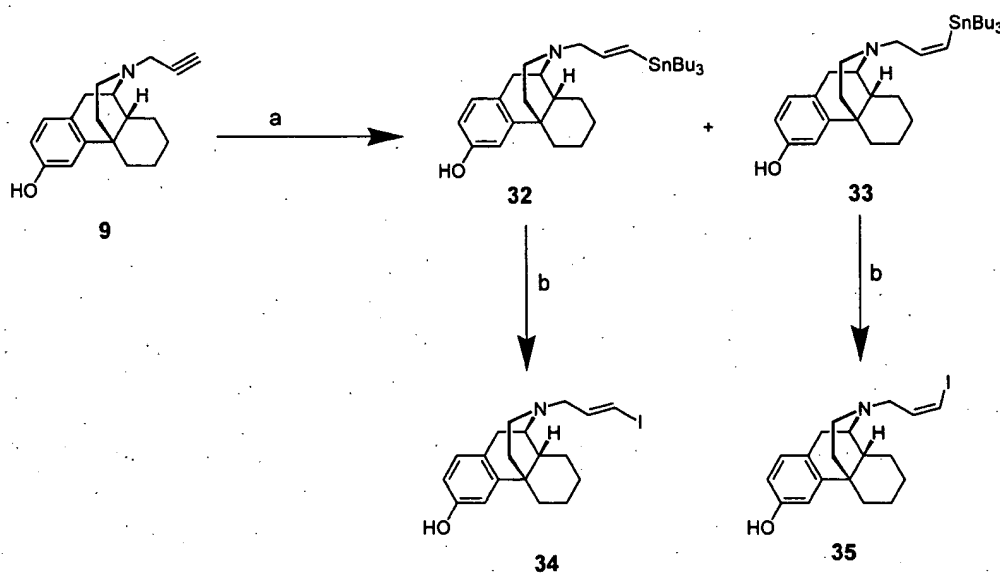
catalyst followed by column separation of the two isomers.<sup>34</sup> Another efficient route to the (*E*)-tributyltin precursor 32 involved alkylation of norlevorphanol with 3-(tributylstannyl)prop-(2*E*)-enyl chloride, which was prepared by chlorination of 3-(tributylstannyl)prop-(2*E*)-en-1-ol with  $PPh_3$  and  $CCl_4$ . The (*E*)-stannyl alcohol was obtained by hydrostannylation of propargyl alcohol using the literature procedure.<sup>35</sup> The structures and physical properties of these new *N*-substituted derivatives are shown in Table 1.

The binding affinities of compounds 3–13, 20–31, and 34–35 for the  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors were assessed using competitive binding assays in guinea pig brain membranes employing [ $^3H$ ]DAMGO ( $\mu$  agonist), [ $^3H$ ]naltrindole ( $\delta$  antagonist) and [ $^3H$ ]U69593 ( $\kappa$  agonist) as radioligands as described previously.<sup>30</sup> The results are summarized in Table 2. For comparison purposes the binding data for U50,488, Mr2033, EKC, levorphanol, and cyclorphan are also included.

As noted, the *N*-substituent had a significant effect on both the opioid receptor binding affinity and selectivity of these morphinan derivatives. Replacement of the methyl group in levorphanol with a cyclopropylmethyl resulted in greatly increased affinity at the  $\delta$  and  $\kappa$  opioid receptors (20-fold and 40-fold, respectively), while the affinity at the  $\mu$  opioid receptor increased just 2-fold.<sup>30</sup> The interesting pharmacology of the cyclopropylmethyl group is not confined to the morphinan series but is also true for the corresponding benzomorphan and morphine series.<sup>30</sup> The *N*-cyclobutylmethyl derivative MCL-101 showed 30-fold increase in binding affinity at the  $\kappa$  opioid receptor but the increase for the  $\mu$  and  $\delta$  opioid receptors is less pronounced (2-fold and 3-fold, respectively). MCL-101 possessed almost the same affinity for the  $\mu$  and  $\kappa$  opioid receptors as cyclorphan but MCL101 had greater  $\kappa/\delta$  selectivity (18-fold vs 4-fold).<sup>30</sup> Further increasing the size of the ring led to a

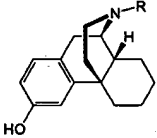


Scheme 1. Reagents and conditions: (a) ethyl chloroformate,  $K_2CO_3$ ,  $CHCl_3$ , reflux; 10% NaOH, MeOH; glacial HOAc, HCl (12 N), reflux; (b) RBr,  $K_2CO_3$  or  $NaHCO_3$ , DMF, rt or 90 °C; (c)  $RCOCl$ ,  $Et_3N$ ,  $CH_2Cl_2$ , 0 °C–rt; (d)  $LiAlH_4$ , THF, rt; (e)  $ArCOCH_2CH_2NMe_3I$ , DMF,  $Na_2CO_3$ , rt; (f)  $NaBH_4$ , MeOH, rt.















Scheme 2. Reagents and conditions: (a)  $\text{Bu}_3\text{SnH}$ ,  $\text{Et}_3\text{B}$ , THF; column separation; (b)  $\text{I}_2$ ,  $\text{CHCl}_3$ .

Table 1. Physical properties of *N*-substituted derivatives of morphinan

						
Compd		R	Molecular formula	Yield (%)	Mp (°C)	Anal. <sup>a</sup>
3	MCL-107	<chem>CCCCF</chem>	$\text{C}_{19}\text{H}_{26}\text{NOF}$	83	215–216 <sup>b</sup>	C, H, N
4	MCL-108	<chem>CCCC(C)C</chem>	$\text{C}_{20}\text{H}_{29}\text{NO} \cdot 0.25\text{H}_2\text{O}$	62	164–165 <sup>c</sup>	C, H, N
5	MCL-109	<chem>CCOC(C)C</chem>	$\text{C}_{20}\text{H}_{29}\text{NO}_2 \cdot 0.5\text{H}_2\text{O}$	69	164–166	C, H, N
6	MCL-110	<chem>CCOC(C)C</chem>	$\text{C}_{19}\text{H}_{27}\text{NO}_2 \cdot 0.75\text{H}_2\text{O}$	95	181–183	C, H, N
7	MCL-111	<chem>c1ccccc1CC</chem>	$\text{C}_{23}\text{H}_{27}\text{NO} \cdot 0.25\text{H}_2\text{O}$	95	165–167	C, H, N
8	MCL-113	<chem>CC=CC</chem>	$\text{C}_{19}\text{H}_{29}\text{NO} \cdot 0.25\text{H}_2\text{O}$	61	172–174	C, H, N
9	MCL-117	<chem>CC#CC</chem>	$\text{C}_{19}\text{H}_{23}\text{NO}$	55	203–204 (dec)	C, H, N
10	MCL-124	<chem>CCCCF3</chem>	$\text{C}_{19}\text{H}_{24}\text{F}_3\text{NO}$	45	Foam	C, H, N
11	MCL-125	<chem>CCCC#N</chem>	$\text{C}_{19}\text{H}_{24}\text{N}_2\text{O} \cdot 0.45\text{H}_2\text{O}$	61	Foam <sup>d</sup>	C, H, N
12	MCL-126	<chem>CCCC#N</chem>	$\text{C}_{20}\text{H}_{26}\text{N}_2\text{O} \cdot 0.25\text{H}_2\text{O}$	75	158–160	C, H, N
13	MCL-127	<chem>CCOC(c1ccccc1)C</chem>	$\text{C}_{24}\text{H}_{29}\text{NO} \cdot 0.25\text{H}_2\text{O}$	56	130–132	C, H, N
20	MCL-104	<chem>CC1(C)CCC1</chem>	$\text{C}_{22}\text{H}_{31}\text{NO}$	68	229–230 <sup>e</sup>	C, H, N

(continued)

Table 1 (continued)

Compd		R	Molecular formula	Yield (%)	Mp (°C)	Anal. <sup>a</sup>
21	MCL-105		C <sub>23</sub> H <sub>33</sub> NO	73	242–243°	C, H, N
22	MCL-119		C <sub>29</sub> H <sub>33</sub> NO <sub>2</sub> ·0.75H <sub>2</sub> O	33	105–110°	C, H, N
23	MCL-120		C <sub>21</sub> H <sub>25</sub> NOS·0.25H <sub>2</sub> O	38	218–220	C, H, N
24	MCL-112		C <sub>24</sub> H <sub>29</sub> NO·0.25H <sub>2</sub> O	39	233–235	C, H, N
26	MCL-114		C <sub>25</sub> H <sub>29</sub> NO <sub>2</sub> ·0.25H <sub>2</sub> O	82	Foam	C, H, N
27	MCL-115		C <sub>25</sub> H <sub>29</sub> NO <sub>2</sub>	76	166–168 (dec)	C, H, N
28	MCL-123		C <sub>23</sub> H <sub>27</sub> NO <sub>3</sub> ·1.25H <sub>2</sub> O	74	Foam	C, H, N
29	MCL-122		C <sub>23</sub> H <sub>29</sub> NO <sub>2</sub> S·1.75H <sub>2</sub> O	64	Foam	C, H, N
30	MCL-121		C <sub>25</sub> H <sub>31</sub> NO <sub>2</sub> ·0.5H <sub>2</sub> O	79	218–220 (dec)	C, H, N
31	MCL-128		C <sub>23</sub> H <sub>29</sub> NO <sub>3</sub>	51	Foam	C, H, N
34	MCL-118		C <sub>19</sub> H <sub>24</sub> INO·0.25H <sub>2</sub> O	32	165–167 (dec)	C, H, N
35	MCL-116		C <sub>19</sub> H <sub>24</sub> INO·0.25H <sub>2</sub> O	15	210–214 (dec)	C, H, N

<sup>a</sup>The C, H, N analyses are within ±0.4% of theoretical values.<sup>b</sup>L-Tartrate salt recrystallized from MeOH.<sup>c</sup>Recrystallized from EtOAc.<sup>d</sup>Jacobson et al.<sup>38</sup> reported that the free base is an oil and the mp of its HCl salt was 188 °C (softening at 160 °C).<sup>e</sup>(S)-Mandelate salt recrystallized from MeOH–PrOH.

loss in binding affinity. The *N*-cyclohexylmethyl derivative 21 (MCL-105) displayed very low affinity for the three opioid receptors. The *N*-isopropyl derivative 4 (MCL-108) showed much higher (14-fold) affinity for the  $\kappa$  receptor but lower (2-fold) affinity for the  $\mu$  receptor than levorphanol. Replacement of the methyl with an allyl group 8 (MCL-113, levallorphan) resulted in 15-fold increase in affinity for the  $\kappa$  opioid receptor and almost no changes in affinity for both of the  $\delta$  and  $\mu$  opioid receptors. Surprisingly, the *N*-propargyl derivative 9 (MCL-117) and the *N*-(3-iodoprop-(2*E*)-enyl) derivative 34 (MCL-118) exhibited unexpectedly high affinity for the  $\mu$  and  $\kappa$  opioid receptors with  $K_i$  values in the picomolar range. In fact, these two compounds are some of the most potent ligands for the  $\mu$  and  $\kappa$  opioid receptors identified to date. Compounds 9 and 34 had the same high affinity for the  $\mu$  opioid receptor but 34 displayed 10-fold decreased affinity for the  $\kappa$  and 43-fold decreased affinity for the  $\delta$  opioid receptor in comparison to 9. The *N*-(3-iodoprop-(2*Z*)-enyl) derivative 35, however, displayed dramatically decreased (100-fold and 17-fold) affinity for the  $\mu$  and  $\kappa$  receptors relative to 34. Recently, May et al. reported the effect on opioid

receptor affinity and efficacy of several *N*-alkenyl and *N*-alkynyl substituents in normetazocine.<sup>36</sup> The *N*-(3-fluoropropyl) derivative 3 (MCL-107) also displayed very high affinity for all three opioid receptors ( $K_i$ =0.18, 0.85, and 0.083 nM for the  $\mu$ ,  $\delta$ , and  $\kappa$  receptor, respectively). The *N*-methoxyethyl derivative 6 (MCL-110) was found to have high affinity for the  $\kappa$  and  $\mu$  opioid receptors ( $K_i$ =0.094 nM and 0.11 nM, respectively). Replacement of methoxyethyl with ethoxyethyl resulted in a 2-fold and 4-fold loss in affinity for the  $\mu$  and  $\kappa$  opioid receptors, respectively. The *N*-phenoxyethyl derivative 13 (MCL-127) exhibited decreased affinity for all three opioid receptors relative to the methoxyethyl derivative 6. It appears that the size of the ether chain affects the affinity for the three opioid receptors. The *N*-methoxymethyl and *N*-fluoropropyl derivatives of normetazocine were found to bind non-selectively, with high affinity for the  $\mu$  and  $\kappa$  receptors.<sup>37</sup> The *N*-furanylmethyl derivative 22 (MCL-119) displayed high affinity for the  $\mu$  and  $\kappa$  receptors ( $K_i$ =0.54 nM and 0.13 nM, respectively). Replacement of the furanylmethyl group with thienylmethyl resulted in decreased affinity for all three opioid receptors but this

Table 2. Opioid receptor binding affinity and selectivity for *N*-substituted derivatives of morphinan

Compd	$K_i$ (nM) $\pm$ SEM			Selectivity	
	[ <sup>3</sup> H]DAMGO ( $\mu$ )	[ <sup>3</sup> H]Naltrindole ( $\delta$ )	[ <sup>3</sup> H]U69,593 ( $\kappa$ )	$\kappa/\mu$	$\kappa/\delta$
U 50,48	220 $\pm$ 5.6	2500 $\pm$ 170	0.36 $\pm$ 0.056	610	6900
Mr2033	0.40 $\pm$ 0.07	4.5 $\pm$ 0.70	0.21 $\pm$ 0.044	2	20
(–)EKC	0.78 $\pm$ 0.10	3.4 $\pm$ 0.41	0.62 $\pm$ 0.11	1	5
Levorphanol	0.21 $\pm$ 0.017	4.2 $\pm$ 2.3	2.3 $\pm$ 0.26	0.09	2
(–) Cyclorphan	0.092 $\pm$ 0.005	0.22 $\pm$ 0.01	0.053 $\pm$ 0.003	2	4
MCL-101	0.12 $\pm$ 0.012	1.3 $\pm$ 0.06	0.073 $\pm$ 0.012	2	18
20 (MCL-104)	0.96 $\pm$ 0.13	6.9 $\pm$ 0.68	0.21 $\pm$ 0.014	5	33
21 (MCL-105)	18 $\pm$ 1.3	69 $\pm$ 5.3	1.5 $\pm$ 0.19	12	46
3 (MCL-107)	0.18 $\pm$ 0.025	0.85 $\pm$ 0.021	0.083 $\pm$ 0.002	2	10
4 (MCL-108)	0.54 $\pm$ 0.15	5.6 $\pm$ 0.70	0.16 $\pm$ 0.25	3	35
5 (MCL-109)	0.26 $\pm$ 0.02	5.6 $\pm$ 0.040	0.33 $\pm$ 0.015	0.8	16
6 (MCL-110)	0.11 $\pm$ 0.007	0.54 $\pm$ 0.05	0.094 $\pm$ 0.001	1	6
7 (MCL-111)	20 $\pm$ 2.9	420 $\pm$ 77	1.9 $\pm$ 0.19	11	220
24 (MCL-112)	0.12 $\pm$ 0.015	3.1 $\pm$ 0.88	1.3 $\pm$ 0.26	0.092	2
8 (MCL-113)	0.34 $\pm$ 0.008	4.1 $\pm$ 0.50	0.16 $\pm$ 0.031	2	26
26 (MCL-114)	0.27 $\pm$ 0.035	10.0 $\pm$ 2.1	4.5 $\pm$ 0.82	0.06	2
27 (MCL-115)	0.43 $\pm$ 0.11	23 $\pm$ 2.6	9.9 $\pm$ 1.2	0.04	2
35 (MCL-116)	0.42 $\pm$ 0.15	33 $\pm$ 6.2	0.65 $\pm$ 0.06	0.6	51
9 (MCL-117)	0.0032 $\pm$ 0.001	0.62 $\pm$ 0.19	0.0030 $\pm$ 0.0005	1	210
34 (MCL-118)	0.0048 $\pm$ 0.001	27 $\pm$ 4.9	0.037 $\pm$ 0.007	0.13	730
22 (MCL-119)	0.54 $\pm$ 0.04	8.5 $\pm$ 1.1	0.13 $\pm$ 0.004	4	65
23 (MCL-120)	1.5 $\pm$ 0.16	51 $\pm$ 6.3	0.32 $\pm$ 0.015	5	160
30 (MCL-121)	21 $\pm$ 8.8	130 $\pm$ 16	57 $\pm$ 2.1	0.4	2
29 (MCL-122)	4.1 $\pm$ 0.27	110 $\pm$ 9.5	25 $\pm$ 0.62	0.2	4
28 (MCL-123)	0.28 $\pm$ 0.06	42 $\pm$ 5.4	7.9 $\pm$ 0.26	0.035	5
10 (MCL-124)	2.3 $\pm$ 0.44	27 $\pm$ 1.7	1.3 $\pm$ 0.10	2	21
11 (MCL-125)	0.33 $\pm$ 0.01	2.6 $\pm$ 0.95	0.23 $\pm$ 0.05	1.4	11
12 (MCL-126)	0.16 $\pm$ 0.02	3.1 $\pm$ 0.38	0.38 $\pm$ 0.008	0.42	8
13 (MCL-127)	0.92 $\pm$ 0.29	33 $\pm$ 1.6	15 $\pm$ 3.6	0.06	2
31 (MCL-128)	4.2 $\pm$ 0.36	29 $\pm$ 2.4	12 $\pm$ 1.9	0.35	2

decrease was most pronounced for the  $\delta$  opioid receptor (6-fold vs 2-fold). Thus, the *N*-thienylmethyl derivative 23 (MCL-120) displayed good selectivity for the  $\mu$  and  $\kappa$  receptors versus  $\delta$  receptor ( $\kappa/\delta = 160$ ,  $\mu/\delta = 14$ ). The *N*-benzyl derivative 7 (MCL-111) showed dramatically decreased affinity at all three opioid receptors relative to 22 and 23. Adding one more carbon between the nitrogen and the phenyl ring (the phenethyl derivative 24) led to a great increase in binding affinity. The increase is 130-fold and 16-fold for the  $\delta$  and  $\mu$  opioid receptors, respectively. The *N*-cyanoethyl derivative 11 (MCL-125), prepared by Jacobson et al. two decades ago,<sup>38</sup> displayed increased affinity (10-fold) for the  $\kappa$  opioid receptor as compared with levorphanol (the *N*-methyl derivative). Replacement of the 2-cyanoethyl with a 3-cyanopropyl group caused few changes in binding affinity for all three opioid receptors. However, the *N*-tri-fluoropropyl derivative 12 had decreased affinity for the  $\mu$  and  $\delta$  receptors and similar affinity for the  $\kappa$  receptor relative to levorphanol. The three Mannich base derivatives 26–28 showed similar binding profiles with good affinity for the  $\mu$  opioid receptor and low affinity for both the  $\kappa$  and  $\delta$  opioid receptors. Reduction of the keto group to secondary alcohol resulted in loss in binding affinity for the three opioid receptors. It seems that a hydroxyl group in the *N*-substituent interferes with the interaction of the ligand with the opioid receptors, probably due to its hydrogen-donating property. Finally, it is important to point out that the  $\kappa/\delta$  selectivity of most of these derivatives was considerably better than that of levorphanol and EKC.

In conclusion, this study demonstrated that the *N*-substituent of morphinan had significant effect on the binding affinity and selectivity for the three opioid receptors. These *N*-substituted derivatives exhibited a strong preference for  $\mu$  and  $\kappa$  versus  $\delta$  binding. The *N*-cyclopropylmethyl (cyclorphan), *N*-(*S*)-tetrahydrofurfuryl,<sup>30</sup> *N*-cyclobutylmethyl (MCL-101),<sup>30</sup> *N*-(3-fluoropropyl) 3 (MCL-107), *N*-methoxyethyl 6 (MCL-110), the *N*-propargyl 9 (MCL-117), and the *N*-(3-iodoprop-(2*E*)-enyl) 34 (MCL-118) derivatives possessed high affinity for the  $\mu$  and  $\kappa$  opioid receptors. In particular, the *N*-propargyl analogue 9 (MCL-117) and the *N*-(3-iodoprop-(2*E*)-enyl) analogue 34 (MCL-118) showed surprisingly high affinity for the  $\mu$  and  $\kappa$  opioid receptors with  $K_i$  values in the picomolar range. Further syntheses of other *N*-substituted derivatives of morphinan and GTP $\gamma$ S functional assays on selected compounds are in progress and will be reported in due course.

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